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Medication Nonadherence After Lung Transplantation in Adult Recipients

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Abstract

Background—Our objective was to identify potential avenues for resource allocation and patient advocacy to improve outcomes by evaluating the association between recipient sociodemographic and patient characteristics and medication nonadherence after lung transplantation.

Methods—States US adult, lung-only transplantations per the United Network for Organ Sharing database were analyzed from October 1996 through December 2006, based on the period during which nonadherence information was recorded. Generalized linear models were used to determine the association of demographic, disease, and transplantation center characteristics with early nonadherence (defined as within the first year after transplantation) as well as late nonadherence (years 2 to 4 after transplantation). Outcomes comparing adherent and nonadherent patients were also evaluated.

Results—Patients (n = 7,284) were included for analysis. Early and late nonadherence rates were 3.1% and 10.6%, respectively. Factors associated with early non-adherence were Medicaid insurance compared with private insurance (adjusted odds ratio [AOR] 2.45, 95% confidence interval [CI]: 1.16 to 5.15), and black race (AOR 2.38, 95% CI: 1.08 to 5.25). Medicaid insurance and black race were also associated with late nonadherence (AOR 2.38, 95% CI: 1.51 to 3.73 and OR 1.73, 95% CI: 1.04 to 2.89, respectively), as were age 18 to 20 years (AOR 3.41, 95% CI: 1.29 to 8.99) and grade school or lower education (AOR 1.88, 95% CI: 1.05 to 3.35). Early and late non-adherence were both associated with significantly shorter unadjusted survival ($p < 0.001$).

Conclusions—Identifying patients at risk of non-adherence may enable resource allocation and patient advocacy to improve outcomes.

In 2011, more than 1,800 lung transplantations were performed in the United States alone [1]. Despite improvements in outcomes after lung transplantation, the 1-year survival remains close to 80% and the median survival is only 5.5 years. Despite immunosuppressive

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drugs, 35% of adult recipients still have at least one episode of acute rejection within the first year [2].

Adherence to medical therapy has repeatedly been shown to be associated with improved outcomes among solid-organ transplant recipients [3–8]. Despite this, non-adherence is a persistent and costly problem in the overall transplantation population [6]. A 2007 meta-analysis found that the incidence of nonadherence was 19% to 25% per year [9]. Of the studies analyzed, only a few reported on lung transplant recipients [10–13]. More recent studies have suggested similar rates of nonadherence in patients who received a lung transplant compared with other solid-organ transplants [14–19]. Furthermore, nonadherence was more common among patients who experienced bronchiolitis obliterans syndrome [20, 21].

Despite this body of evidence regarding the importance of medication adherence in lung transplant recipients, a paucity of literature exists regarding risk factors for nonadherence in this patient population. Furthermore, medication nonadherence has been recognized as not only related to factors on an individual level but also results from failings of the health system related to health access, cost, and communication [22–25]. Our objective was to evaluate the association between recipient socio-demographic and disease characteristics and the incidence of nonadherence after lung transplantation using a cohort of all lung transplantations performed in the United States. A secondary objective was to report the survival implications of nonadherence after lung transplantation.

Patients and Methods

The Institutional Review Board at Duke University Medical Center approved this study.

Study Population

The Organ Procurement and Transplantation Network's national computerized database as maintained by the United Network of Organ Sharing (UNOS) was used for this analysis [26]. This contains data regarding every organ donation and transplantation event occurring in the United States since October 1, 1987 [1]. The dataset used for the present study included lung transplantations performed through December 31, 2011, with follow-up through March 31, 2012. All adult (≥18 years) lung transplant recipients were included for analysis. Multiple organ, en block, lobar, and repeat transplantations were excluded. The study period included transplantations performed from October 1996 through December 2006 based on the time period during which nonadherence information was recorded in the UNOS database. To be included in the study, patients had to have a follow-up visit after transplantation documenting the presence or absence of evidence of noncompliance with immuno-suppressive medication during this follow-up period that compromised the patient's recovery within the first 4 years after transplantation (this is a yes/no field on the Adult Thoracic Transplant Recipient Follow-Up Worksheet [Office of Management and Budget approved form number 0915-0157]). Patients with unknown or missing adherence information were excluded.

Variable Definitions

The UNOS database includes donor, recipient, and transplantation-related characteristics. To describe our study cohort, we included the following characteristics: age; sex; race; cause of lung failure; diabetes; hypertension; creatinine; body mass index, steroid use before transplantation that required life support at the time of transplantation; Lung Allocation Score (available after May 2005); days on the waitlist; insurance carrier; education level; smoking history; type of transplantation; human leukocyte antigen mismatch level; donor/recipient sex, race, and cytomegalovirus (CMV) mismatch; total ischemic time (hours); transplantation year; and transplantation center volume.

PREDICTOR VARIABLES—Predictor variables for analysis were determined a priori based on factors previously demonstrated in the literature to affect medication adherence [8, 16, 25, 27–29]. These variables included recipient age, sex, race, smoking history, insurance carrier, education level, cause of lung failure, comorbidities, year of transplantation, and transplantation center volume.

OUTCOME MEASURES AND FOLLOW-UP—The primary outcome variable was nonadherence with immunosuppressive medications. This was separately assessed for non-adherence within the first year (termed early non-adherence) and nonadherence during years 2 to 4 (termed late nonadherence). To be included in an analysis for a given postoperative period (early or late) a patient must have had definitive documentation of the presence or absence of nonadherence during that time. Overall survival for patients with nonadherence was also assessed in comparison with patients without nonadherence. Outcome data for each patient were ascertained from the date of transplantation until patient death, date of last follow-up, or the end of study period (March 31, 2012).

Study Design and Statistical Analysis

We performed a retrospective, observational cohort analysis of lung transplant recipients subject to inclusion/exclusion criteria as described in the sections above. Baseline characteristics were described for the overall study population, with medians and interquartile range (IQR) reported for continuous variables and proportions (frequency, percentage) for discrete variables.

Multivariable logistic regression was performed to assess the association between predictor variables defined in the section above and nonadherence with immunosuppressive medications. Logistic regression models were performed separately for early and late nonadherence. The late nonadherence models included transplantations before year 2003 to allow adequate follow-up time to assess late nonadherence. Continuous variables included in the model (recipient age, year of transplantation, and transplantation center volume) were assessed for linearity with respect to the outcome measures. Only recipient age demonstrated a nonlinear relation and was accordingly stratified by age 18 to 20 years, 21 to 50 years, and 51 years and older.

To assess survival implications of nonadherence, unadjusted patient survival rates for early and late non-adherence were estimated using the product-limit (Kaplan-Meier) method [30]

and compared with control subjects using the log-rank test. Patients with early non-adherence were excluded from the analysis of late non-adherence to isolate the association of late nonadherence with survival.

Statistical analyses were performed using JMP Version 10.0 (SAS Institute Inc, Cary, NC) and R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). For all comparisons, p values less than or equal to 0.05 were considered statistically significant, and all tests were two sided.

Results

Study Population and Baseline Characteristics

A total of 7,284 lung transplant recipients met the inclusion and exclusion criteria of this study (Fig 1). Median recipient age was 54 years (IQR, 44 to 60 years), whereas median donor age was 29 years (IQR, 20 to 44 years) (Table 1). Most of the lung transplant recipients were white (n = 6,472, 88.9%), whereas 490 (6.7%) recipients were black, 233 (3.2%) recipients were Hispanic. Private insurance/self-payment was the most frequent recipient insurance at time of transplantation (n = 4,556, 63.0) followed by Medicare (n = 1,789, 24.7%) and Medicaid (n = 529, 7.3%) (Table 2).

Early and Late Nonadherence

Factors associated with early nonadherence were Medicaid insurance (adjusted odds ratio [AOR] compared with private insurance/self-pay 2.45, 95% confidence interval [CI]: 1.16 to 5.15, $p = 0.019$), and black race (AOR compared with white 2.38, 95% CI: 1.08 to 5.25, $p = 0.031$). Medicaid insurance and black race were also associated with late nonadherence (AOR 2.38, 95% CI: 1.51 to 3.73, $p < 0.001$ and AOR 1.73, 95% CI: 1.04 to 2.89, $p = 0.035$, respectively). Additional factors associated with late nonadherence included age 18 to 20 years (AOR compared with age 21 to 50 years 3.41, 95% CI: 1.29 to 8.99, $p = 0.013$) and grade school or lower education (AOR compared with high school or equivalent diploma 1.88, 95% CI: 1.05 to 3.35, $p = 0.034$; Table 3). Patients aged 51 years and older demonstrated a significantly decreased risk of early nonadherence (AOR compared with age 21 to 50 years 0.43, 95% confidence interval: 0.23 to 0.77, $p = 0.005$) and late nonadherence (AOR 0.57, 95% CI: 0.41 to 0.79, $p < 0.001$).

Overall Survival

Survival of patients with early nonadherence was significantly shorter than control subjects (median survival, 2.25 versus 5.67 years, log-rank test: $p < 0.001$) (Fig 2). After excluding patients with early nonadherence, patients with late nonadherence also demonstrated a lower survival rate than control subjects (median survival, 5.6 versus 7.4 years, log-rank test: $p < 0.001$) (Fig 3).

Comment

Adherence to medication regimens has long been recognized as an important component to length and quality of life not only for lung transplant recipients but also across the health

care spectrum. There are clear implications for clinical outcomes, as well as added cost associated with avoidable hospitalizations and other preventable consequences of lapses in medical therapy [22, 23]. Data reported from all transplantation centers in the United States demonstrated that more than 10% of those patients struggle with taking their immunosuppressive medications, with early nonadherence being less prevalent than late nonadherence. Age between 18 and 20 years, black race, Medicaid insurance, and grade school or lower education were identified as independent risk factors for nonadherence. Early and late nonadherence was shown to be associated with shorter survival after lung transplantation than patients without reported nonadherence.

Barriers to adherence are frequently intertwined with intrinsic deficiencies of the health care system, including limited access to care, prohibitive cost, and failures in communication [22]. Given that the recipients' abilities to address these barriers are limited, resources allocated to improving adherence should focus on high-risk populations who are the most likely to benefit from their use [24]. Furthermore, the international guidelines for selection of candidates for lung transplantation states that documented nonadherence or inability to follow through with medical therapy or office follow-up or both is an absolute contraindication for lung transplantation [31]. This further emphasizes the importance of better understanding factors contributing to nonadherence to ensure that patients are not denied this life-saving intervention due to failings of the health system.

Our data suggest that younger patients have an independent increased risk of nonadherence, which confirms earlier findings in lung transplant recipients [16]. Similar influences are likely contributing to nonadherence observed in the young adults included in our study population. Similarly to our findings, adolescent age, black race, and Medicaid insurance have shown an association with nonadherence in pediatric heart transplant recipients [32, 33]. In addition, the biology and human leukocyte antigen status of different racial groups [34–37] may lead to increased rates of graft dysfunction, rejection, or both being misinterpreted as nonadherence. It should also be acknowledged that those recording nonadherence may introduce a racial bias in determining whether a decline in clinical status for a given patient is assumed to be due to lack of medication adherence.

Low income as well as high-cost medication regimens (as is the situation with transplant recipients) have been demonstrated to correlate with medication nonadherence as well as potentially harmful strategies to cope with medication costs, such as underdosing, delaying refills, or skipping doses [22, 38, 39]. However, nonadherence has been demonstrated to occur despite full coverage of medication cost [40], reinforcing the multidimensional nature of nonadherence incorporating factors such as cognitive impairment, depression, lack of insight or asymptomatic disease or both, side effects, inadequate follow-up or discharge planning, and poor provider-patient communication [22].

The strong association with worse survival after transplantation in our study population underscores the importance of systematically addressing nonadherence. This is independent of whether patients showed early or late nonadherence. In the lung transplantation setting, it is well documented that reduced immunosuppressive drug levels after transplantation are associated with chronic allograft rejection, especially bronchiolitis obliterans syndrome [20].

The importance of adherence to immunosuppressive medications has also been documented in other solid-organ transplantations, with studies reporting up to a sevenfold increase in graft loss among nonadherent recipients [5]. Not only is non-adherence associated with potentially preventable deaths, but there are also implications for cost to the health care system and allocation of resources. In a review of adherence to medication by Osterberg and Blaschke [22], it was estimated that more than $100 billion are spent each year on avoidable hospitalizations from non-adherence, demonstrating that the problem does not only exist in the transplantation setting but throughout medicine.

Advances in information technology may hold promise for improvement in medication adherence by effectively monitoring, interfacing, and engaging patients with their regimens. Many interventions to help patients with medication adherence are currently under investigation, including hand-held computer-based interventions [38], text messaging [39], and electronic medication tracking devices [40]. Although results of these investigations are encouraging, it is increasingly perceived that interventions will have to be specifically tailored to individual needs in coordination with provider relationships, communication, and scheduled follow-up.

Limitations

In UNOS, the reporting of nonadherence is based on the discretion of each reporting facility and was not necessarily assessed in a formal and structured interview. As such, this may be an insensitive measure to adequately capture the full spectrum of nonadherent patients. Similarly, nonadherent patients without any adverse consequences are less likely to be detected. Still, the prevalence of more than 10% in the UNOS patient cohort is in line with other reports that range from 4.5% to 26% [9, 12, 15–17].

As a further limitation, information about non-adherence may be poorly reported, was only recorded until December 2006 (not allowing for a more recent analysis) and was not assessed based on severity of nonadherence. Different age cut-off values may have been used by other investigators in such analysis. Finally, by the retrospective nature of this analysis, inherent unmeasured potential confounders such as information on psychosocial characteristics, income, distance of living to medical facilities, and living in rural versus urban areas may exist.

Conclusions

In summary, we have found that age, race, insurance status, and education level were associated with non-adherence, which subsequently portends a decrease in survival after transplantation. This information should help identify patients at increased risk before transplantation to increase awareness and to put in place efficient strategies to assist patients in their efforts to remain adherent to medication regimens. We would advocate that the medical community should resume collecting information about adherence in a structured way because such an investment would likely pay dividends in increased survival and improved quality of life for lung transplant recipients.

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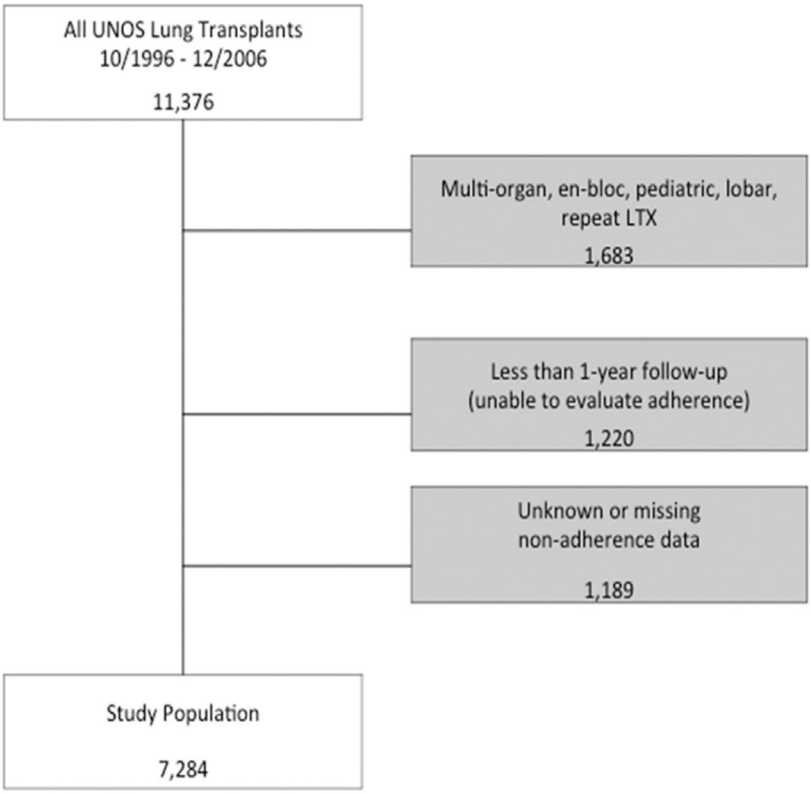

Fig 1.

Study inclusion algorithm. (LTX = lung transplantation; UNOS = United Network of Organ Sharing.)

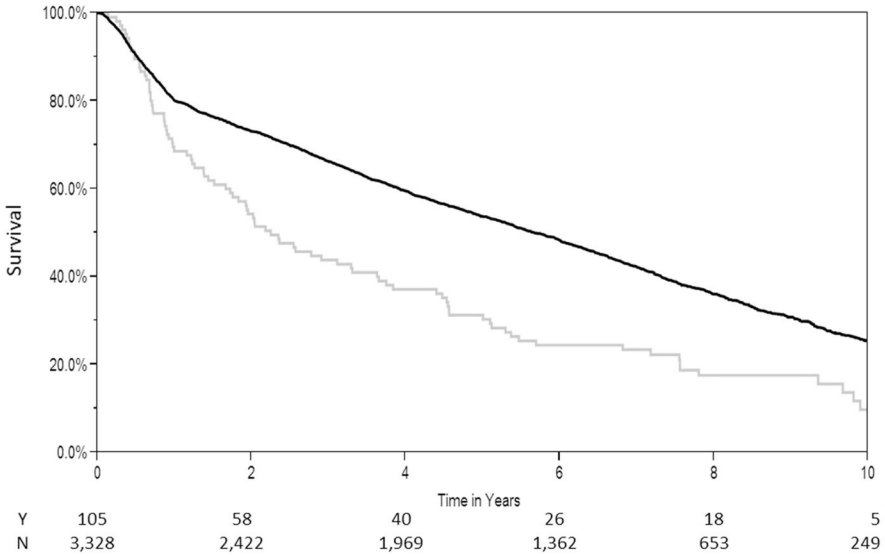

Fig 2.
Unadjusted Kaplan-Meier survival curves. (N = no; Y = yes.)

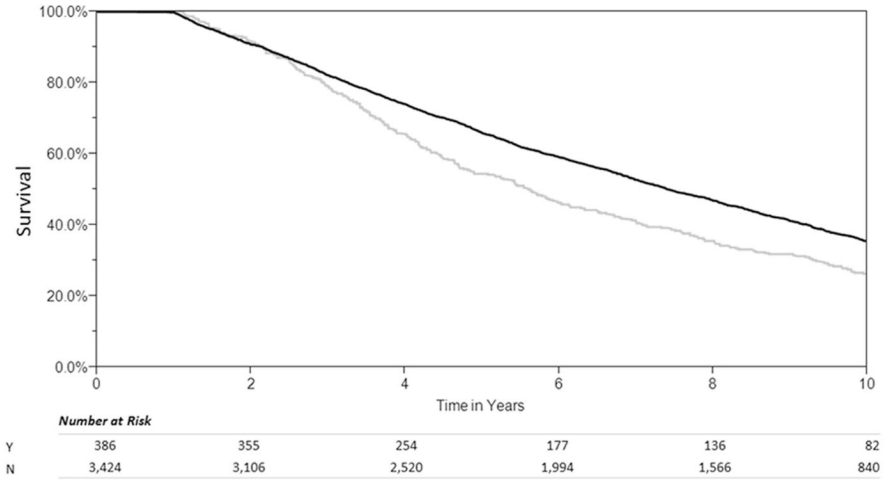

Fig 3.

Late nonadherence (within years 2 to 4 after transplantation). (N = no; Y = yes.)

Table 1

Baseline Characteristics for the Entire Cohort (n = 7,284)

Characteristic	Value
Donor characteristics	
Donor age, years	29 (20–44)
Donor diabetes	235 (3.2)
Donor smoking history (>20 pack-years ever)	1,819 (25.2)
Donor cocaine use (ever)	518/5,564 (9.3)
Terminal serum creatinine, mg/dL	0.9 (0.7–1.2)
Donor BMI, kg/m^2	23.8 (21.3–26.8)
PO_2 on 100% inspired oxygen (n = 5,390)	455 (383–514)
Recipient characteristics	
Age, years	54 (44–60)
Age ≥ 60 years	1,919 (26.4)
Female sex	3,561 (48.9)
Race	
White	6,472 (88.9)
Black	490 (6.7)
Hispanic	233 (3.2)
Asian	54 (0.7)
Other/unknown	35 (0.5)
Cause of lung failure	
Obstructive disease	4,110 (56.8)
Restrictive disease	1,836 (25.4)
CF or immunodeficiency	1,023 (14.1)
Pulmonary vascular disease	273 (3.8)
Comorbidities	
Diabetes	631 (8.8)
Hypertension	1,141 (16)
Cerebrovascular disease	50 (0.7)
Creatinine at transplantation, mg/dL	0.8 (0.7–1.0)
BMI at transplantation, kg/m^2	23.7 (20.2–27.2)
Chronic steroid use before transplantation	3,396/6,831 (49.7)
Status before transplantation	
Hospitalized	293 (4)
Intensive care unit	163 (2.2)
Requiring life support at transplantation[a]	300 (4.1)
Ventilator dependent at transplantation	124 (1.7)
Lung allocation score (n = 827)	36.3 (33.4–42.0)
Pulmonary function and hemodynamics	
Oxygen requirement, L (n = 6,376)	2 (2–3)
FEV_1, % predicted (n = 6,695)	25 (18–45)

Characteristic	Value
FVC, % predicted (n = 6,671)	49 (38–61)
FEV/FVC (n = 6,648)	0.56 (0.39–0.98)
Mean PA pressure, mm Hg (n = 5,002)	25 (20–30)
PVR, Wood units (n = 4,270)	2.6 (1.8–3.6)
Cardiac index, L/min/m^2 (n = 4,713)	2.8 (2.4–3.4)
Days on waitlist	312 (112–656)
Transplantation characteristics	
Bilateral transplantation	3,358 (46.1)
HLA mismatch level 3+	5,655/5,890 (96)
Donor/recipient sex mismatch	2,321 (31.9)
Donor/recipient race mismatch	2,354 (32.3)
Donor/recipient CMV mismatch	1,113/5,194 (21.4)
Ischemic time, hours (n = 6,369)	4.5 (3.4–5.6)

[a] Includes ventilator, extracorporeal membrane oxygenation, intravenous inotropes, intra-aortic balloon pump, or inhaled nitric oxide.

Values are expressed as median (IQR), n (%), or n/N (%).

BMI = body mass index; CF = cystic fibrosis; CMV = cytomegalovirus; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HLA = human leukocyte antigen; IQR = interquartile range; PA = pulmonary pressure; PO_2 = partial pressure of oxygen; PVR = pulmonary vascular resistance.

Table 2

Recipient Socioeconomic Characteristics (n = 7,284)

Characteristic	Value
Recipient insurance at time of transplantation	
Private/self	4,556 (63.0)
Medicaid	529 (7.3)
Medicare	1,789 (24.7)
Other	360 (5.0)
Education level	
Grade school or lower	190/6,112 (3.1)
High school or GED	2,893/6,112 (47.3)
Attended college or technical school (no degree)	1,578/6,112 (25.8)
College degree or higher	1,451/6,112 (23.7)
Smoking history (>10 pack years)	4,137/5,968 (69.3)

Values are expressed as n (%) or n/N (%).

GED = General Educational Development.

Table 3

Multivariable Logistic Regression for Patient Nonadherence Based on Secondary Predictor Variables

	Early Nonadherence		Late Nonadherence[a]	
Demographic and Socioeconomic Characteristics	**AOR (95% CI)**	***p* Value**	**AOR (95% CI)**	***p* Value**
Age (reference: 21–50 years [n = 2,596])				
18–20 years (n = 138)	3.34 (0.93–11.94)	0.064	3.41 (1.29–8.99)	0.013
≥51 years (n = 4,550)	0.43 (0.23–0.77)	0.005	0.57 (0.41–0.79)	0.001
Female sex	0.81 (0.49–1.34)	0.410	0.84 (0.64–1.12)	0.240
Ethnicity (reference: white)				
Black	2.38 (1.08–5.25)	0.031	1.73 (1.04–2.89)	0.035
Hispanic/Asian/other/unknown	1.26 (0.36–4.36)	0.714	0.42 (0.13–1.37)	0.151
Cause of lung failure (reference: obstructive disease)				
Restrictive disease	0.70 (0.35–1.39)	0.302	0.84 (0.55–1.27)	0.399
CF or immunodeficiency	0.87 (0.31–2.42)	0.789	1.21 (0.60–2.46)	0.592
Pulmonary vascular disease	0.35 (0.04–2.71)	0.312	0.96 (0.39–2.36)	0.926
Chronic comorbidities (DM or HTN)	1.34 (0.77–2.34)	0.295	0.89 (0.62–1.28)	0.524
Smoking history (>10 pack years)	1.41 (0.65–3.04)	0.383	1.57 (0.93–2.65)	0.088
Insurance status (reference = private/self)				
Medicaid	2.45 (1.16–5.15)	0.019	2.38 (1.51–3.73)	0.001
Medicare	1.41 (0.78–2.54)	0.252	1.26 (0.90–1.75)	0.180
Other	1.91 (0.71–5.11)	0.198	0.56 (0.26–1.24)	0.156
Education level (reference: high school or equivalent diploma)				
Grade school or lower	1.08 (0.31–3.81)	0.904	1.88 (1.05–3.35)	0.034
Attended college or technical school	1.15 (0.63–2.09)	0.653	0.92 (0.65–1.32)	0.660
College degree or higher	1.33 (0.69–2.59)	0.394	1.29 (0.89–1.88)	0.172
Year of transplantation (AOR per year increase)	0.80 (0.71–0.90)	<0.001	0.89 (0.80–0.98)	0.016
Center volume (AOR per increase of 10/year)	1.01 (0.87–1.18)	0.902	1.07 (0.98–1.16)	0.129

[a] Includes ventilator, extracorporeal membrane oxygenation, intravenous inotropes, intra-aortic balloon pump, or inhaled nitric oxide.

AOR = adjusted odds ratio; CF = cystic fibrosis; CI = confidence interval; DM = diabetes mellitus; HTN = hypertension.